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(54) Title: NITROSATED AND/OR NITROSYLATED URSODEOXYCHOLIC ACID COMPOUNDS, COMPOSITIONS AND METHODS OF USE

(57) Abstract: The invention describes nitrosated and/or nitrosylated ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, and novel compositions comprising at least one nitrosated and/or nitrosylated ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or at least one therapeutic agent. The invention also provides novel compositions comprising at least one ursodeoxycholic acid compound, or an made or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, and at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or at least one therapeutic agent. The invention also provides novel kits comprising at least one ursodeoxycholic acid compound, that is optionally nitrosated and/or nitrosylated, and, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent. The invention also provides methods for treating and/or preventing portal hypertension, liver diseases, reflux, gastritis, inflammatory conditions of the gastrointestinal tract, coronary heart diseases, neurological or cognitive conditions or for lowering cholesterol levels.

# NITROSATED AND/OR NITROSYLATED URSODEOXYCHOLIC ACID COMPOUNDS, COMPOSITIONS AND METHODS OF USE

## RELATED APPLICATIONS

This application claims priority to U. S. Application No. 60/401,036, filed August 6, 2002.

## FIELD OF THE INVENTION

The invention describes nitrosated and/or nitrosylated ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, and novel compositions comprising at least one nitrosated and/or nitrosylated ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or at least one therapeutic agent. The invention also provides novel compositions comprising at least one ursodeoxycholic acid compound, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, and at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or at least one therapeutic agent. The invention also provides novel kits comprising at least one ursodeoxycholic acid compound, that is optionally nitrosated and/or nitrosylated, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent. The invention also provides methods for treating and/or preventing portal hypertension, liver diseases, reflux, gastritis, inflammatory conditions of the gastrointestinal tract, coronary heart diseases, neurological or cognitive conditions or for lowering cholesterol levels.

## BACKGROUND OF THE INVENTION

Portal hypertension resulting from increased intrahepatic resistance is a common complication of chronic liver diseases and a leading cause of death in patients with liver cirrhosis, a scarring process of the liver that includes components of both increased fibrogenesis and wound contraction. A reduced production of nitric oxide (NO) resulting from an impaired enzymic function of endothelial NO synthase and an increased contraction of hepatic stellate cells (HSCs) have been shown to contribute to high intrahepatic resistance in the cirrhotic liver.

There is still a need in the art for novel ursodeoxycholic acid compounds that can treat and/or prevent portal hypertension, liver diseases, reflux, gastritis, inflammatory conditions of the gastrointestinal tract, coronary heart diseases, neurological and cognitive conditions or lower cholesterol levels, and that can be used at low dosages. The invention is directed to these, as well as other, important ends.

## SUMMARY OF THE INVENTION

The invention provides novel compounds that are nitrosated and/or nitrosylated ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically

acceptable salts thereof. The ursodeoxycholic acid compounds, or an amide, sulfate conjugate or a pharmaceutically acceptable salt thereof, can be nitrosated and/or nitrosylated through one or more sites, such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen. The invention also provides compositions comprising the novel compounds described herein in a pharmaceutically acceptable carrier.

The invention is also based on the discovery that administering at least one ursodeoxycholic acid compound, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, that is optionally substituted with at least one NO and/or $NO_2$ group (i.e., nitrosylated and/or nitrosated), and, optionally, at least one nitric oxide donor can be used to treat and/or prevent portal hypertension, liver diseases, reflux, gastritis, inflammatory conditions of the gastrointestinal tract, coronary heart diseases, neurological or cognitive conditions or for lowering cholesterol levels. Nitric oxide donors include, for example, S-nitrosothiols, nitrites, nitrates, N-oxo-N-nitrosamines, SPM 3672, SPM 5185, SPM 5186 and analogues thereof, and substrates of the various isozymes of nitric oxide synthase. Thus, another aspect of the invention provides compositions comprising at least one ursodeoxycholic acid compound, or an amide or sulfate conjugate thereof, that is optionally substituted with at least one NO and/or $NO_2$ group (i.e., nitrosylated and/or nitrosated), and at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium ($NO^+$) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase. The invention also provides for such compositions in a pharmaceutically acceptable carrier.

Another aspect of the invention provides compositions comprising a therapeutically effective amount of at least one ursodeoxycholic acid compound, or an amide or sulfate conjugate thereof, that is optionally substituted with at least one $NO_2$ group and/or at least one NO group (i.e., nitrosated and/or nitrosylated respectively), and, optionally, at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium ($NO^+$) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase, and/or, optionally, at least one therapeutic agent, including but not limited to, steroids, nonsteroidal antiinflammatory compounds (NSAID), cyclooxygenase-2 (COX-2) inhibitors, 5-lipoxygenase (5-LO) inhibitors, leukotriene $B_4$ ($LTB_4$) receptor antagonists, leukotriene $A_4$ ($LTA_4$) hydrolase inhibitors, 5-HT agonists, HMG CoA inhibitors, $H_2$ antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and the like. The invention also provides for such compositions in a pharmaceutically acceptable carrier.

Yet another embodiment of the invention provides methods for treating and/or preventing portal hypertension, liver diseases, reflux, gastritis, inflammatory conditions of the gastrointestinal

tract, coronary heart diseases, neurological or cognitive conditions or for lowering cholesterol levels in a patient in need thereof which comprises administering to the patient a therapeutically effective amount of at least one ursodeoxycholic acid compound, or an amide or sulfate conjugate thereof, that is optionally substituted with at least one $NO_2$ group and/or at least one NO group (i.e., nitrosated and/or nitrosylated), and, optionally, at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium ($NO^+$) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase (i.e., NO donors). The methods can optionally further comprise the administration of at least one therapeutic agent, such as, for example, steroids, nonsteroidal antiinflammatory compounds (NSAID), cyclooxygenase-2 (COX-2) inhibitors, 5-lipoxygenase (5-LO) inhibitors, leukotriene $B_4$ ($LTB_4$) receptor antagonists, leukotriene $A_4$ ($LTA_4$) hydrolase inhibitors, 5-HT agonists, HMG CoA inhibitors, $H_2$ antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures of two or more thereof. In this aspect of the invention, the methods can involve administering the nitrosated and/or nitrosylated ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, administering the ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, that are optionally nitrosated and/or nitrosylated, and NO donors; administering the ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, that are optionally nitrosated and/or nitrosylated, and therapeutic agents, or administering the ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, that are optionally nitrosated and/or nitrosylated, NO donors and therapeutic agents. The ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

In yet another aspect the invention provides kits comprising at least one ursodeoxycholic acid compound, or an amide or sulfate conjugate thereof, that is optionally substituted with at least one $NO_2$ group and/or at least one NO group (i.e., nitrosated and/or nitrosylated respectively), and, optionally, at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium ($NO^+$) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase. The kit can further comprise at least one therapeutic agent, such as, for example, steroids, nonsteroidal antiinflammatory compounds (NSAID), cyclooxygenase-2 (COX-2) inhibitors, 5-lipoxygenase (5-LO) inhibitors, leukotriene $B_4$ ($LTB_4$) receptor antagonists, leukotriene $A_4$ ($LTA_4$) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, $H_2$ antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase

inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures of two or more thereof. The ursodeoxycholic acid compound, or an amide or sulfate conjugate thereof, the nitric oxide donor and/or therapeutic agent, can be separate components in the kit or can be in the form of a composition in the kit in one or more pharmaceutically acceptable carriers.

## DETAILED DESCRIPTION OF THE INVENTION

As used throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

"Liver disease or disorder" refers to any liver disease or disorder known in the art, including, but not limited to liver fibrosis, hepatitis (e.g., hepatitis A, B, C, D), biliary calculosis, biliary dyscinesia, nonalcoholic steatohepatitis, alcoholic liver disease, Wilson's disease, acute liver failure, chronic liver injury, cholestatic liver diseases, such as for example, cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune cholangitis, and the like.

"Inflammatory conditions of the gastrointestinal tract" refers to colon cancer, rectum cancer, neoplasm of the colon, a neoplasm of the rectum, carcinogenesis of the colon, carcinogenesis of the rectum, ulcerative colitis, an adenomatous polyp, familial polyposis, and the like.

"Neurological or cognitive conditions" refers to stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, AIDs-induced dementia, epilepsy, alcoholism, alcohol withdrawal, drug-induced seizures, viral, bacterial or fever-induced seizure, trauma to the head, hypoglycemia, hypoxia, myocardial infarction, cerebral vascular hemorrhage, hemorrhage, dementia of all types, drug-induced brain damage, aging and the like.

" Coronary heart disease " refers to any cardiovascular disease or disorder known in the art, including, but not limited to, restenosis, atherosclerosis, atherogenesis, angina, (particularly chronic, stable angina pectoris), ischemic disease, congestive heart failure or pulmonary edema associated with acute myocardial infarction, thrombosis, controlling blood pressure in hypertension (especially hypertension associated with cardiovascular surgical procedures), thromboembolic events, platelet aggregation, platelet adhesion, smooth muscle cell proliferation, hypercholesterolemia, hyperlipidemia, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, cerebrovascular ischemic events, and the like. Complications associated with the use of medical devices may occur as a result of increased platelet deposition, activation, thrombus formation or consumption of platelets and coagulation proteins. Such complications, which are within the definition of "cardiovascular disease or disorder," include, for example, myocardial infarction, ischemic stroke, transient ischemic stroke, thromboembolic events, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, thrombocytopenia, bleeding disorders and/or any other complications which occur either directly or indirectly as a result of the foregoing disorders.

"Restenosis" is a cardiovascular disease or disorder that refers to the closure of a peripheral or

coronary artery following trauma to the artery caused by an injury such as, for example, angioplasty, balloon dilation, atherectomy, laser ablation treatment or stent insertion. Restenosis can also occur following a number of invasive surgical techniques, such as, for example, transplant surgery, vein grafting, coronary artery bypass surgery, endarterectomy, heart transplantation, balloon angioplasty, atherectomy, laser ablation, endovascular stenting, and the like.

"Atherosclerosis" is a form of chronic vascular injury in which some of the normal vascular smooth muscle cells in the artery wall, which ordinarily control vascular tone regulating blood flow, change their nature and develop "cancer-like" behavior. These vascular smooth muscle cells become abnormally proliferative, secreting substances such as growth factors, tissue-degradation enzymes and other proteins, which enable them to invade and spread into the inner vessel lining, blocking blood flow and making that vessel abnormally susceptible to being completely blocked by local blood clotting, resulting in the death of the tissue served by that artery. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all common manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease".

"Thromboembolic events" includes, but is not limited to, ischemic stroke, transient ischemic stroke, myocardial infarction, angina pectoris, thrombosis, thromboembolism, thrombotic occlusion and reocclusion, acute vascular events, restenosis, transient ischemic attacks, and first and subsequent thrombotic stroke. Patients who are at risk of developing thromboembolic events, may include those with a familial history of, or genetically predisposed to, thromboembolic disorders, who have had ischemic stroke, transient ischemic stroke, myocardial infarction, and those with unstable angina pectoris or chronic stable angina pectoris and patients with altered prostacyclin/thromboxane $A_2$ homeostasis or higher than normal thromboxane $A_2$ levels leading to increase risk for thromboembolism, including patients with diabetes and rheumatoid arthritis.

"Platelet aggregation" refers to the binding of one or more platelets to each other. Platelet aggregation is commonly referred to in the context of generalized atherosclerosis, not with respect to platelet adhesion on vasculature damaged as a result of physical injury during a medical procedure. Platelet aggregation requires platelet activation which depends on the interaction between the ligand and its specific platelet surface receptor.

"Platelet activation" refers either to the change in conformation (shape) of a cell, expression of cell surface proteins (e.g., the IIb/IIIa receptor complex, loss of GPIb surface protein), and secretion of platelet derived factors (e.g., serotonin, growth factors).

"Therapeutic agent" includes any therapeutic agent that can be used to treat or prevent the diseases described herein. "Therapeutic agents" include, for example, steroids, nonsteroidal antiinflammatory compounds, cyclooxygenase-2 inhibitors, 5-lipoxygenase inhibitors, leukotriene $B_4$ receptor antagonists, leukotriene $A_4$ hydrolase inhibitors, 3-hydroxy-3-methylglutaryl coenzyme A

inhibitors, $H_2$ antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and the like. Therapeutic agent includes the pro-drugs and pharmaceutical derivatives thereof including but not limited to the corresponding nitrosated and/or nitrosylated derivatives. Although nitric oxide donors have therapeutic activity, the term "therapeutic agent" does not include the nitric oxide donors described herein, since nitric oxide donors are separately defined.

"Thromboxane inhibitor" refers to any compound that reversibly or irreversibly inhibits thromboxane synthesis, and includes compounds which are the so-called thromboxane $A_2$ receptor antagonists, thromboxane $A_2$ antagonists, thromboxane $A_2$/prostaglandin endoperoxide antagonists, thromboxane receptor (TP) antagonists, thromboxane antagonists, thromboxane synthase inhibitors, and dual acting thromboxane synthase inhibitors and thromboxane receptor antagonists. The characteristics of the preferred thromboxane inhibitor should include the suppression of thromboxane $A_2$ formation (thromboxane synthase inhibitors) and/or blockade of thromboxane $A_2$ and prostaglandin $H_2$ platelet and vessel wall (thromboxane receptor antagonists). The effects should block platelet activation and therefore platelet function.

"Thromboxane $A_2$ receptor antagonist" refers to any compound that reversibly or irreversibly blocks the activation of any thromboxane $A_2$ receptor.

"Thromboxane synthase inhibitor" refers to any compound that reversibly or irreversibly inhibits the enzyme thromboxane synthesis thereby reducing the formation of thromboxane $A_2$. Thromboxane synthase inhibitors may also increase the synthesis of antiaggregatory prostaglandins including prostacyclin and prostaglandin $D_2$. Thromboxane $A_2$ receptor antagonists and thromboxane synthase inhibitors and can be identified using the assays described in Tai, Methods of Enzymology, Vol. 86, 110-113 (1982); Hall, *Medicinal Research Reviews,* 11:503-579 (1991) and Coleman et al., *Pharmacol Rev.*, 46: 205-229 (1994) and references therein, the disclosures of which are incorporated herein by reference in its entirety.

"Dual acting thromboxane receptor antagonist and thromboxane synthase inhibitor" refers to any compound that simultaneously acts as a thromboxane $A_2$ receptor antagonist and a thromboxane synthase inhibitor.

"Thrombin inhibitors" refers to and includes compounds that inhibit hydrolytic activity of thrombin, including the catalytic conversion of fibrinogen to fibrin, activation of Factor V to Va, Factor VIII to VIIIa, Factor XIII to XIIIa and platelet activation. Thrombin inhibitors may be identified using assays described in Lewis et at., Thrombosis Research. 70: 173-190 (1993).

"NSAID" refers to a nonsteroidal anti-inflammatory compound or a nonsteroidal anti-inflammatory drug. NSAIDs inhibit cyclooxygenase, the enzyme responsible for the biosyntheses of the prostaglandins and certain autocoid inhibitors, including inhibitors of the various isozymes of cyclooxygenase (including but not limited to cyclooxygenase-1 and -2), and as inhibitors of both

cyclooxygenase and lipoxygenase.

"Cyclooxygenase-2 (COX-2) selective inhibitor" refers to a compound that selectively inhibits the cyclooxygenase-2 enzyme over the cyclooxygenase-1 enzyme. In one embodiment, the compound has a cyclooxygenase-2 $IC_{50}$ of less than about 2 μM and a cyclooxygenase-1 $IC_{50}$ of greater than about 5 μM, in the human whole blood COX-2 assay (as described in Brideau et al., *Inflamm Res.*, 45: 68-74 (1996)) and also has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 10, and preferably of at least 40. In another embodiment, the compound has a cyclooxygenase-1 $IC_{50}$ of greater than about 1 μM, and preferably of greater than 20 μM. The compound can also inhibit the enzyme, lipoxygenase. Such selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

"Patient" refers to animals, preferably mammals, most preferably humans, and includes males and females, and children and adults.

"Therapeutically effective amount" refers to the amount of the compound and/or composition that is effective to achieve its intended purpose.

"Transdermal" refers to the delivery of a compound by passage through the skin and into the blood stream.

"Transmucosal" refers to delivery of a compound by passage of the compound through the mucosal tissue and into the blood stream.

"Penetration enhancement" or "permeation enhancement" refers to an increase in the permeability of the skin or mucosal tissue to a selected pharmacologically active compound such that the rate at which the compound permeates through the skin or mucosal tissue is increased.

"Carriers" or "vehicles" refers to carrier materials suitable for compound administration and include any such material known in the art such as, for example, any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is non-toxic and which does not interact with any components of the composition in a deleterious manner.

"Nitric oxide adduct" or "NO adduct" refers to compounds and functional groups which, under physiological conditions, can donate, release and/or directly or indirectly transfer any of the three redox forms of nitrogen monoxide ($NO^+$, $NO^-$, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide releasing" or "nitric oxide donating" refers to methods of donating, releasing and/or directly or indirectly transferring any of the three redox forms of nitrogen monoxide ($NO^+$, $NO^-$, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide donor" or "NO donor" refers to compounds that donate, release and/or directly or indirectly transfer a nitrogen monoxide species, and/or stimulate the endogenous production of nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* and/or elevate endogenous levels of nitric oxide or EDRF *in vivo*. "NO donor" also includes compounds that are substrates for nitric

oxide synthase.

"Alkyl" refers to a lower alkyl group, a haloalkyl group, a hydroxyalkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein. An alkyl group may also comprise one or more radical species, such as, for example a cycloalkylalkyl group or a heterocyclicalkyl group.

"Lower alkyl" refers to branched or straight chain acyclic alkyl group comprising one to about ten carbon atoms (preferably one to about eight carbon atoms, more preferably one to about six carbon atoms). Exemplary lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, iso-amyl, hexyl, octyl, and the like.

"Substituted lower alkyl" refers to a lower alkyl group, as defined herein, wherein one or more of the hydrogen atoms have been replaced with one or more $R^{100}$ groups, wherein each $R^{100}$ is independently a hydroxy, an oxo, a carboxyl, a carboxamido, a halo, a cyano or an amino group, as defined herein.

"Haloalkyl" refers to a lower alkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein, to which is appended one or more halogens, as defined herein. Exemplary haloalkyl groups include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloro-pentyl, and the like.

"Alkenyl" refers to a branched or straight chain $C_2$-$C_{10}$ hydrocarbon (preferably a $C_2$-$C_8$ hydrocarbon, more preferably a $C_2$-$C_6$ hydrocarbon) that can comprise one or more carbon-carbon double bonds. Exemplary alkenyl groups include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexan-1-yl, hepten-1-yl, octen-1-yl, and the like.

"Lower alkenyl" refers to a branched or straight chain $C_2$-$C_4$ hydrocarbon that can comprise one or two carbon-carbon double bonds.

"Substituted alkenyl" refers to a branched or straight chain $C_2$-$C_{10}$ hydrocarbon (preferably a $C_2$-$C_8$ hydrocarbon, more preferably a $C_2$-$C_6$ hydrocarbon) which can comprise one or more carbon-carbon double bonds, wherein one or more of the hydrogen atoms have been replaced with one or more $R^{100}$ groups, wherein each $R^{100}$ is independently a hydroxy, an oxo, a carboxyl, a carboxamido, a halo, a cyano or an amino group, as defined herein.

"Alkynyl" refers to an unsaturated acyclic $C_2$-$C_{10}$ hydrocarbon (preferably a $C_2$-$C_8$ hydrocarbon, more preferably a $C_2$-$C_6$ hydrocarbon) that can comprise one or more carbon-carbon triple bonds. Exemplary alkynyl groups include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyl-1-yl, pentyl-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyl-2-yl, hexyl-3-yl, 3,3-dimethyl-butyn-1-yl, and the like.

"Bridged cycloalkyl" refers to two or more cycloalkyl groups, heterocyclic groups, or a combination thereof fused via adjacent or non-adjacent atoms. Bridged cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, carboxyl, alkylcarboxylic acid, aryl, amidyl,

ester, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. Exemplary bridged cycloalkyl groups include adamantyl, decahydronapthyl, quinuclidyl, 2,6-dioxabicyclo(3.3.0)octane, 7-oxabycyclo(2.2.1)heptyl, 8-azabicyclo(3,2,1)oct-2-enyl and the like.

"Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon comprising from about 3 to about 10 carbon atoms. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, aryl, amidyl, ester, hydroxy, halo, carboxyl, alkylcarboxylic acid, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo, alkylsulfinyl, and nitro. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like.

"Heterocyclic ring or group" refers to a saturated or unsaturated cyclic hydrocarbon group having about 2 to about 10 carbon atoms (preferably about 4 to about 6 carbon atoms) where 1 to about 4 carbon atoms are replaced by one or more nitrogen, oxygen and/or sulfur atoms. Sulfur maybe in the thio, sulfinyl or sulfonyl oxidation state. The heterocyclic ring or group can be fused to an aromatic hydrocarbon group. Heterocyclic groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylthio, aryloxy, arylthio, arylalkyl, hydroxy, oxo, thial, halo, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, amidyl, ester, alkylcarbonyl, arylcarbonyl, alkylsulfinyl, carboxamido, alkylcarboxamido, arylcarboxamido, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary heterocyclic groups include pyrrolyl, furyl, thienyl, 3-pyrrolinyl,4,5,6-trihydro-2H-pyranyl, pyridinyl, 1,4-dihydropyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrhydrofuranyl, tetrazolyl, pyrrolinyl, pyrrolindinyl, oxazolindinyl 1,3-dioxolanyl, imidazolinyl, imidazolindinyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, benzothiazolinyl, quinolinyl, and the like.

"Heterocyclic compounds" refer to mono- and polycyclic compounds comprising at least one aryl or heterocyclic ring.

"Aryl" refers to a monocyclic, bicyclic, carbocyclic or heterocyclic ring system comprising one or two aromatic rings. Exemplary aryl groups include phenyl, pyridyl, napthyl, quinoyl, tetrahydronaphthyl, furanyl, indanyl, indenyl, indoyl, and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, alkylthio, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, halo, cyano, alkylsulfinyl, hydroxy, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, alkylcarbonyl, arylcarbonyl, amidyl, ester, carboxamido, alkylcarboxamido, carbomyl, sulfonic acid, sulfonic ester, sulfonamido

and nitro. Exemplary substituted aryl groups include tetrafluorophenyl, pentafluorophenyl, sulfonamide, alkylsulfonyl, arylsulfonyl, and the like.

"Cycloalkenyl" refers to an unsaturated cyclic $C_2$-$C_{10}$ hydrocarbon (preferably a $C_2$-$C_8$ hydrocarbon, more preferably a $C_2$-$C_6$ hydrocarbon) which can comprise one or more carbon-carbon triple bonds.

"Alkylaryl" refers to an alkyl group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary alkylaryl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl, and the like.

"Arylalkyl" refers to an aryl radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary arylalkyl groups include benzyl, phenylethyl, 4-hydroxybenzyl, 3-fluorobenzyl, 2-fluorophenylethyl, and the like.

"Arylalkenyl" refers to an aryl radical, as defined herein, attached to an alkenyl radical, as defined herein. Exemplary arylalkenyl groups include styryl, propenylphenyl, and the like.

"Cycloalkylalkyl" refers to a cycloalkyl radical, as defined herein, attached to an alkyl radical, as defined herein.

"Cycloalkylalkoxy" refers to a cycloalkyl radical, as defined herein, attached to an alkoxy radical, as defined herein.

"Cycloalkylalkylthio" refers to a cycloalkyl radical, as defined herein, attached to an alkylthio radical, as defined herein.

"Heterocyclicalkyl" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein.

"Arylheterocyclic ring" refers to a bi- or tricyclic ring comprised of an aryl ring, as defined herein, appended via two adjacent carbon atoms of the aryl ring to a heterocyclic ring, as defined herein. Exemplary arylheterocyclic rings include dihydroindole, 1,2,3,4-tetra-hydroquinoline, and the like.

"Alkylheterocyclic ring" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary alkylheterocyclic rings include 2-pyridylmethyl, 1-methylpiperidin-2-one-3-methyl, and the like.

"Alkoxy" refers to $R_{50}O$-, wherein $R_{50}$ is an alkyl group, as defined herein (preferably a lower alkyl group or a haloalkyl group, as defined herein). Exemplary alkoxy groups include methoxy, ethoxy, t-butoxy, cyclopentyloxy, trifluoromethoxy, and the like.

"Aryloxy" refers to $R_{55}O$-, wherein $R_{55}$ is an aryl group, as defined herein. Exemplary arylkoxy groups include napthyloxy, quinolyloxy, isoquinolizinyloxy, and the like.

"Alkylthio" refers to $R_{50}S$-, wherein $R_{50}$ is an alkyl group, as defined herein.

"Lower alkylthio" refers to a lower alkyl group, as defined herein, appended to a thio group, as defined herein.

"Arylalkoxy" or "alkoxyaryl" refers to an alkoxy group, as defined herein, to which is

appended an aryl group, as defined herein. Exemplary arylalkoxy groups include benzyloxy, phenylethoxy, chlorophenylethoxy, and the like.

"Alkoxyalkyl" refers to an alkoxy group, as defined herein, appended to an alkyl group, as defined herein. Exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, isopropoxymethyl, and the like.

"Alkoxyhaloalkyl" refers to an alkoxy group, as defined herein, appended to a haloalkyl group, as defined herein. Exemplary alkoxyhaloalkyl groups include 4- methoxy-2-chlorobutyl and the like.

"Cycloalkoxy" refers to $R_{54}O$-, wherein $R_{54}$ is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkoxy groups include cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

"Cycloalkylthio" refers to $R_{54}S$-, wherein $R_{54}$ is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkylthio groups include cyclopropylthio, cyclopentylthio, cyclohexylthio, and the like.

"Haloalkoxy" refers to an alkoxy group, as defined herein, in which one or more of the hydrogen atoms on the alkoxy group are substituted with halogens, as defined herein. Exemplary haloalkoxy groups include 1,1,1-trichloroethoxy, 2-bromobutoxy, and the like.

"Hydroxy" refers to -OH.

"Oxo " refers to =O.

"Oxy " refers to $-O^- R_{77}^+$ wherein $R_{77}$ is an organic or inorganic cation.

"Oxime" refers to $=N\text{-}OR_{81}$ wherein $R_{81}$is a hydrogen, an alkyl group, an aryl group, an alkylsulfonyl group, an arylsulfonyl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxyalkyl group or an alkoxyaryl group.

"Hydrazone refers to $=N\text{-}N(R_{81})(R'_{81})$ wherein $R'_{81}$ is independently selected from $R_{81}$, and $R_{81}$ is as defined herein.

"Organic cation" refers to a positively charged organic ion. Exemplary organic cations include alkyl substituted ammonium cations, and the like.

"Inorganic cation" refers to a positively charged metal ion. Exemplary inorganic cations include Group I metal cations such as for example, sodium, potassium, and the like.

"Hydroxyalkyl" refers to a hydroxy group, as defined herein, appended to an alkyl group, as defined herein.

"Nitrate" refers to $-O\text{-}NO_2$.

"Nitrite" refers to -O-NO.

"Thionitrate" refers to $-S\text{-}NO_2$.

"Thionitrite" and "nitrosothiol" refer to -S-NO.

"Nitro" refers to the group $-NO_2$ and "nitrosated" refers to compounds that have been substituted therewith.

"Nitroso" refers to the group -NO and "nitrosylated" refers to compounds that have been substituted therewith.

"Nitrile" and "cyano" refer to -CN.

"Halogen" or "halo" refers to iodine (I), bromine (Br), chlorine (Cl), and/or fluorine (F).

"Amino " refers to $-NH_2$, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein.

"Alkylamino" refers to $R_{50}NH-$, wherein $R_{50}$ is an alkyl group, as defined herein. Exemplary alkylamino groups include methylamino, ethylamino, butylamino, cyclohexylamino, and the like.

"Arylamino" refers to $R_{55}NH-$, wherein $R_{55}$ is an aryl group, as defined herein.

"Dialkylamino" refers to $R_{52}R_{53}N-$, wherein $R_{52}$ and $R_{53}$ are each independently an alkyl group, as defined herein. Exemplary dialkylamino groups include dimethylamino, diethylamino, methyl propargylamino, and the like.

"Diarylamino" refers to $R_{55}R_{60}N-$, wherein $R_{55}$ and $R_{60}$ are each independently an aryl group, as defined herein.

"Alkylarylamino or arylalkylamino" refers to $R_{52}R_{55}N-$, wherein $R_{52}$ is an alkyl group, as defined herein, and $R_{55}$ is an aryl group, as defined herein.

"Alkylarylalkylamino " refers to $R_{52}R_{79}N-$, wherein $R_{52}$ is an alkyl group, as defined herein, and $R_{79}$ is an arylalkyl group, as defined herein.

"Alkylcycloalkylamino " refers to $R_{52}R_{80}N-$, wherein $R_{52}$ is an alkyl group, as defined herein, and $R_{80}$ is an cycloalkyl group, as defined herein.

"Aminoalkyl " refers to an amino group, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein, to which is appended an alkyl group, as defined herein. Exemplary aminoalkyl groups include dimethylaminopropyl, diphenylaminocyclopentyl, methylaminomethyl, and the like.

"Aminoaryl " refers to an aryl group to which is appended an alkylamino group, a arylamino group or an arylalkylamino group. Exemplary aminoaryl groups include anilino, N-methylanilino, N-benzylanilino, and the like.

"Thio" refers to –S-.

"Sulfinyl" refers to -S(O)-.

"Methanthial" refers to -C(S)-.

"Thial" refers to =S.

"Sulfonyl" refers to $-S(O)_2-$.

"Sulfonic acid" refers to $-S(O)_2OR_{76}$, wherein $R_{76}$ is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Alkylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an aryl group, as defined herein

"Sulfonic ester" refers to $-S(O)_2OR_{58}$, wherein $R_{58}$ is an alkyl group, an aryl group, or an aryl heterocyclic ring, as defined herein.

"Sulfonamido" refers to $-S(O)_2-N(R_{51})(R_{57})$, wherein $R_{51}$ and $R_{57}$ are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or $R_{51}$ and $R_{57}$ when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an aryl group, as defined herein.

"Alkylthio" refers to $R_{50}S-$, wherein $R_{50}$ is an alkyl group, as defined herein (preferably a lower alkyl group, as defined herein).

"Arylthio" refers to $R_{55}S-$, wherein $R_{55}$ is an aryl group, as defined herein.

"Arylalkylthio" refers to an aryl group, as defined herein, appended to an alkylthio group, as defined herein.

"Alkylsulfinyl" refers to $R_{50}-S(O)-$, wherein $R_{50}$ is an alkyl group, as defined herein.

"Alkylsulfonyl" refers to $R_{50}-S(O)_2-$, wherein $R_{50}$ is an alkyl group, as defined herein.

"Alkylsulfonyloxy" refers to $R_{50}-S(O)_2-O-$, wherein $R_{50}$ is an alkyl group, as defined herein.

"Arylsulfinyl" refers to $R_{55}-S(O)-$, wherein $R_{55}$ is an aryl group, as defined herein.

"Arylsulfonyl" refers to $R_{55}-S(O)_2-$, wherein $R_{55}$ is an aryl group, as defined herein.

"Arylsulfonyloxy" refers to $R_{55}-S(O)_2-O-$, wherein $R_{55}$ is an aryl group, as defined herein.

"Amidyl" refers to $R_{51}C(O)N(R_{57})-$ wherein $R_{51}$ and $R_{57}$ are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein.

"Ester" refers to $R_{51}C(O)O-$ wherein $R_{51}$ is a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein.

"Carbamoyl" refers to $-O-C(O)N(R_{51})(R_{57})$, wherein $R_{51}$ and $R_{57}$ are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or $R_{51}$ and $R_{57}$ taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Carboxyl" refers to $-C(O)OR_{76}$, wherein $R_{76}$ is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Carbonyl" refers to –C(O)-.

"Alkylcarbonyl" refers to $R_{52}-C(O)-$, wherein $R_{52}$ is an alkyl group, as defined herein.

"Arylcarbonyl" refers to $R_{55}-C(O)-$, wherein $R_{55}$ is an aryl group, as defined herein.

"Arylalkylcarbonyl" refers to $R_{55}$-$R_{52}$-C(O)-, wherein $R_{55}$ is an aryl group, as defined herein, and $R_{52}$ is an alkyl group, as defined herein.

"Alkylarylcarbonyl" refers to $R_{52}$-$R_{55}$-C(O)-, wherein $R_{55}$ is an aryl group, as defined herein, and $R_{52}$ is an alkyl group, as defined herein.

"Heterocyclicalkylcarbonyl" refer to $R_{78}$C(O)- wherein $R_{78}$ is a heterocyclicalkyl group, as defined herein.

"Carboxylic ester" refers to -C(O)O$R_{58}$, wherein $R_{58}$ is an alkyl group, an aryl group or an aryl heterocyclic ring, as defined herein.

"Alkylcarboxylic acid" and "alkylcarboxyl" refer to an alkyl group, as defined herein, appended to a carboxyl group, as defined herein.

"Alkylcarboxylic ester" refers to an alkyl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Arylcarboxylic acid" refers to an aryl group, as defined herein, appended to a carboxyl group, as defined herein.

"Arylcarboxylic ester" and "arylcarboxyl" refer to an aryl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Carboxamido" refers to -C(O)N($R_{51}$)($R_{57}$), wherein $R_{51}$ and $R_{57}$ are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or $R_{51}$ and $R_{57}$ when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylcarboxamido" refers to an alkyl group, as defined herein, appended to a carboxamido group, as defined herein.

"Arylcarboxamido" refers to an aryl group, as defined herein, appended to a carboxamido group, as defined herein.

"Urea" refers to -N($R_{59}$)-C(O)N($R_{51}$)($R_{57}$) wherein $R_{51}$, $R_{57}$, and $R_{59}$ are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or $R_{51}$ and $R_{57}$ taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Phosphoryl" refers to -P($R_{70}$)($R_{71}$)($R_{72}$), wherein $R_{70}$ is a lone pair of electrons, thial or oxo, and $R_{71}$ and $R_{72}$ are each independently a covalent bond, a hydrogen, a lower alkyl, an alkoxy, an alkylamino, a hydroxy, an oxy or an aryl, as defined herein.

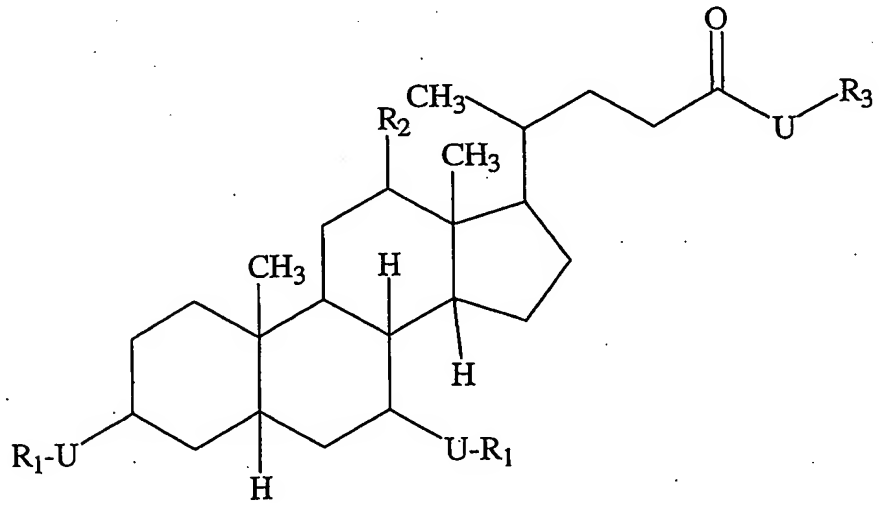
"Silyl" refers to -Si($R_{73}$)($R_{74}$)($R_{75}$), wherein $R_{73}$, $R_{74}$ and $R_{75}$ are each independently a covalent bond, a lower alkyl, an alkoxy, an aryl or an arylalkoxy, as defined herein.

Compounds that donate, transfer or release nitric oxide species *in vivo* have been recognized as having a wide spectrum of advantages and applications. The invention is based on the unexpected discovery of the effects of such compounds alone and together with one or more ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, for the treatment or prevention of portal

hypertension, liver diseases, reflux, gastritis, inflammatory conditions of the gastrointestinal tract, coronary heart diseases, neurological or cognitive conditions or for lowering cholesterol levels can be obtained by the use of ursodeoxycholic acid compounds of the invention; or by the use of ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, in conjunction with one or more compounds that donate, release or transfer nitric oxide and/or stimulate endogenous production of NO and/or EDRF *in vivo* and/or is a substrate for nitric oxide synthase, and, optionally, with one or more therapeutic agents.

The ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, that are optionally nitrosated and/or nitrosylated, can be used alone or in conjunction with one or more compounds that donate, release or transfer nitric oxide and/or stimulate endogenous production of NO and/or EDRF *in vivo* and/or is a substrate for nitric oxide synthase, and/or with one or more therapeutic agents, such as for example, steroids, nonsterodal antiinflammatory compounds (NSAID), cyclooxygenase-2 (COX-2) inhibitors, 5-lipoxygenase (5-LO) inhibitors, leukotriene $B_4$ ($LTB_4$) receptor antagonists, leukotriene $A_4$ ($LTA_4$) hydrolase inhibitors, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, $H_2$ antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures of two or more thereof. These novel compounds and novel compositions of the present invention are described in more detail herein.

In one embodiment, the invention describes ursodeoxycholic acid compounds of Formula (I), or an amide or sulfate conjugate thereof, and pharmaceutically acceptable salts thereof:




I

wherein:

$R_1$ is a hydrogen, carboxylic ester group, a lower alkyl group or $D_1$;

$R_2$ is a hydrogen, an alkoxy group or $-OD_1$;

$R_3$ is a hydrogen, a lower alkyl group, V or K;

$D_1$ is a hydrogen, V or K;

V is—NO or $-NO_2$;

U is an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$;

K is $-W_{aa}-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-U-V$;

wherein aa, b, c, d, g, i and j are each independently an integer from 0 to 3;

p, x, y and z are each independently an integer from 0 to 10;

W at each occurrence is independently -C(O)-, -C(S)-, -T-, $-(C(R_e)(R_f))_h-$, an alkyl group, an aryl group, a heterocyclic ring, an arylheterocyclic ring, $-(CH_2CH_2O)_q-$ or a covalent bond;

E at each occurrence is independently a -T- group, an alkyl group, an aryl group, a heterocyclic ring, $-(C(R_e)(R_f))_h-$, an arylheterocyclic ring or $-(CH_2CH_2O)_q-$;

h is an integer form 1 to 10;

q is an integer from 1 to 5;

$R_e$ and $R_f$ are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -U-V, or $-(C(R_g)(R_h))_k-U-V$ or $R_e$ and $R_f$ taken together are an oxo, a thial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group;

$R_g$ and $R_h$ at each occurrence are independently $R_e$;

k is an integer from 1 to 3;

T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$,

o is an integer from 0 to 2,

$R_a$ is a lone pair of electrons, a hydrogen or an alkyl group;

$R_i$ is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-OR'_i$, $-CH_2-C(U-V)(R_g)(R_h)$, a bond to an adjacent atom creating a double bond to that atom or $-(N_2O_2-)^-\bullet M^+$, wherein $M^+$ is an organic or inorganic cation; with the proviso that when $R_i$ is $-CH_2-C(U-V)(R_e)(R_f)$ or $-(N_2O_2-)\bullet M^+$; then "-U-V" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group;

$R'_i$ is independently selected from $R_i$; and

with the proviso that the compounds of Formula I must contain least one of a nitrite, a nitrate, a thionitrite ester or a thionitrate ester.

In cases where $R_e$ and $R_f$ are a heterocyclic ring or $R_e$ and $R_f$ taken together with the carbon atom to which they are attached are a heterocyclic ring, then $R_i$ can be a substituent on any disubstituted nitrogen contained within the radical where $R_i$ is as defined herein.

In cases where multiple designations of variables that reside in sequence are chosen as a "covalent bond" or the integer chosen is 0, the intent is to denote a single covalent bond connecting one radical to another. For example, $E_0$ would denote a covalent bond, while $E_2$ denotes (E-E) and $(C(R_e)(R_f))_2$ denotes $-C(R_e)(R_f)-C(R_e)(R_f)-$.

In a preferred embodiment the compounds of Formula (I) do not include the compounds of ACS registry numbers 510728-21-9, 349487-19-0, 349481-67-0, 294191-01-8, 301828-27-3, 301828-26-2, 294191-01-8, 124119-82-0, 122387-47-7, 122387-37-5, 120910-03-4, 120498-93-3, 117884-50-1, 103005-02-3, 64219-17-6, 15241-87-9, 15073-15-1, 14943-00-1, 14942-97-3, 14942-96-2, 14942-93-9. These compounds are disclosed in, for example, U.S. Patent No. 6,310,052, 5,807,847 and 5,883,122; and in WO 01/49275, WO 00/61604, WO 00/54756 and in Fiorucci et al., *Proc. Natl. Acad. Sci.*, 98:8897-8902 (2001); Fiorucci et al., *Proc. Natl. Acad. Sci.*, 98:2652-2657 (2001); Dias et al., *Spctrochimica Acta*. Part A: 56A: 53-77 (2000); Lee et al., *Tet. Letts.*, 39:873-876 (1998); Mihaesi, *Chemica*, 39:223-230 (1994), Albert et al., *Revista Medicala.*, 25:127-132 (1979), Dias et al., *J. Org. Chem.*, 44:4572-4577 (1979); Dias et al., *J. Chem. Eng. News.*, 22:445-447 (1977); Hodosan et al., *Revue Roumaine de Chimie.*, 14:509-516 (1969); Hodosan et al., *Roumaine de Chimie.*, 11:983-991 (1966); Tanasescu et al., *Acad. Rep. Populare Romine Filiala* 11:315-323 (1960); Ganea et al., *Chimie*, 1:117-120 (1961); the disclosures of each of which are incorporated herein in their entirety.

In another embodiment the invention describes compounds of Formulas (I) that are sulfate conjugates or amide conjugates of ursodeoxycholic acid. The sulfate conjugates include ursodeoxycholic acid-3-sulfate, ursodeoxycholic acid-7-sulfate, ursodeoxycholic acid-3,7-disulfate, glyco- ursodeoxycholic acid-3-sulfate, glyco- ursodeoxycholic acid-7-sulfate, glyco- ursodeoxycholic acid,3,7-disulfate, tauro-ursodeoxycholic acid-3-sulfate, tauro-ursodeoxycholic acid-7-sulfate, tauro-ursodeoxycholic acid,3,7-disulfate, and mixture of two or more thereof. Suitable sulfate conjugates of ursodeoxycholic acid and amide conjugates of ursodeoxycholic acid are described in U.S. Patent No. 6,251,884 B1, and in WO 97/34608, the disclosures of each of which are incorporated herein by reference in their entirety.

In another embodiment of the invention describes compounds of Formulas (I), and pharmaceutically acceptable salts thereof, that each must contain at least one NO and/or $NO_2$ group (i.e., nitrosylated and/or nitrosated) wherein the one NO and/or $NO_2$ group is linked to the compounds of Formula (I) through one or more sites, such as oxygen (hydroxyl condensation), sulfur (sulfhydryl

condensation) and/or nitrogen.

Another embodiment of the invention describes the metabolites of the compounds of Formulas (I), and pharmaceutically acceptable salts thereof. These metabolites, include but are not limited to, the non-nitrosated and/or non-nitrosylated derivatives, degradation products, hydrolysis products, and the like, of the compounds of Formulas (I), and pharmaceutically acceptable salts thereof.

Compounds of the invention that have one or more asymmetric carbon atoms may exist as the optically pure enantiomers, pure diastereomers, mixtures of enantiomers, mixtures of diastereomers, racemic mixtures of enantiomers, diastereomeric racemates or mixtures of diastereomeric racemates. The invention includes within its scope all such isomers and mixtures thereof.

Another embodiment of the invention provides processes for making the novel compounds of the invention and to the intermediates useful in such processes. The reactions are performed in solvents appropriate to the reagents and materials used are suitable for the transformations being effected. It is understood by one skilled in the art of organic synthesis that the functionality present in the molecule must be consistent with the chemical transformation proposed. This will, on occasion, necessitate judgment by the routineer as to the order of synthetic steps, protecting groups required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described, but alternative methods and substituents compatible with the reaction conditions will be readily apparent to one skilled in the art. The use of sulfur and oxygen protecting groups is well known for protecting thiol and alcohol groups against undesirable reactions during a synthetic procedure and many such protecting groups are known and described by, for example, Greene and Wuts, *Protective Groups in Organic Synthesis*, Third Edition, John Wiley & Sons, New York (1999).

The chemical reactions described herein are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by one skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to one skilled in the art, *e.g.*, by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily prepared from known starting materials.

The synthesis of the ursodeoxycholic acid compounds (i.e. non-nitrosated and non-nitrosylated ursodeoxycholic acid compounds) are disclosed in, for U.S. Patent Nos. 4,379,093, 4,440,688, 4,579,819, 4,828,763, 4,865,765, 5,310,560, 6,075,132, 6,251,884, and in WO 90/00175, WO 97/18816, WO 97/34608, and WO 99/16429, the disclosures of each of which are incorporated

herein in their entirety.

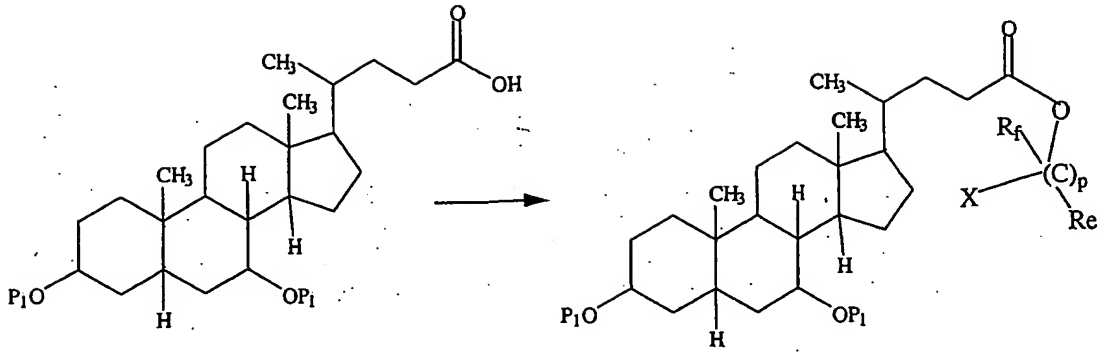
The nitrosated and nitrosylated ursodeoxycholic acid compounds of the invention can be synthesized as shown in Scheme 1 herein. The parent ursodeoxycholic acid compounds can be nitrosated and/or nitrosylated through one or more sites such as oxygen, sulfur, and/or nitrogen using the methods described in the examples herein and using conventional methods known to one skilled in the art. For example, known methods for nitrosating and nitrosylating compounds are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; WO 00/61604 and Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety. The methods of nitrosating and/or nitrosylating the compounds described in the examples herein and in these references can be applied by one skilled in the art to produce any of the nitrosated and/or nitrosylated ursodeoxycholic acid compounds described herein.

Nitroso or nitro compounds of Formula (I), where X is a –ONO, -SNO, or $-ONO_2$ group, $P_1$is an oxygen protecting group, and $R_e$, $R_f$, and p, are as defined herein, and a nitrite, nitrate, or thionitrite containing carboxylic acid ester is representative of the K group may be prepared as shown in Scheme 1. The acid of the Formula (I) is converted to the ester of Formula **IA, IB**, or **IC**, where $P_1$, p, $R_e$, $R_f$ and X are as defined herein, by reaction with an appropriate nitrite, thionitrite, or nitrate containing alcohol. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of **1** with a chloroformate, such as isobutylchloroformate, in the presence of a non-nucleophilic base, such as triethylamine, in an anhydrous inert solvent, such as dichloromethane, diethylether or THF. The mixed anhydride is then reacted with the nitrite, thionitrite, or nitrate containing alcohol preferably in the presence of a condensation catalyst, such as DMAP. Alternatively, the acid **1** may be first converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the nitrite, thionitrite, or nitrate containing alcohol preferably in the presence of a condensation catalyst, such as DMAP, and a tertiary amine base, such as triethylamine, to afford the ester of Formula **IA, IB**, or **IC**. Alternatively, the acid **1** and nitrite, thionitrite, or nitrate containing alcohol may be coupled to afford the ester of Formula **IA, IB**, or **IC** by treatment with a dehydrating agent, such as DCC or EDAC·HCl, with or without a catalyst, such as DMAP or HOBt.

On occasion it might be desirable to nitrosylate the alcohol or thiol after coupling the acid to the alcohol. The ester would be prepared by reacting the carboxylic acid with an alcohol containing a protected alcohol or thiol moiety. Preferred protecting groups for an alcohol moiety are silyl ethers, such as a trimethylsilyl ether, a tert-butyldimethylsilyl ether, or a tert-butyldiphenylsilyl ether. After coupling the acid and alcohol moieties, deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine, gives the compound of Formula **IA**. Preferred

protecting groups for the thiol moiety are as a thioester, such as a thioacetate or a thiobenzoate or as a disulfide. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base or sodium methoxide in methanol is typically used to hydrolyze thioesters) followed by reaction with a suitable nitrosylating agent such, as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite, such as tert-butyl nitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as methylene chloride, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine, gives the compound of Formula **IB**. Nitrosation of the ester product containing a deprotected alcohol moiety may be accomplished by first converting the alcohol to a leaving group, such as a mesylate or a tosylate. This reaction is typically performed at a temperature of 0 $^{0}$C to room temperature in an inert solvent, such as ether, THF, or dichloromethane with the alcohol, methansulfonyl chloride or para-toluensulfonyl chloride, and an amine base, such as triethylamine or pyridine, as the reactants. The corresponding iodide is then prepared by reacting the mesylate or tosylate with sodium iodide in acetone. The halide may also be formed from the alcohol by treatment of the hydroxyl moiety with a phosphorus reagent, such as triphenylphosphine, in the presence of a halide source, such as carbon tetrabromide or N-iodosuccinimide, in an inert solvent, such as THF. Treatment of the bromide or iodide with silver nitrate in an inert solvent, such as acetonitrile, affords the compound of Formula **IC**. Alternatively, the halide containing ester may be formed directly by preparing a halide containing active acylating agent from a halide containing acid. Preferred halides are bromide and iodide. Coupling of the alcohol with the halide containing active acylating agent followed by reaction of the ester product with silver nitrate affords the compound of Formula **IC**. Preferred coupling methods for the formation of esters from alcohols are those methods described herein (e.g. with the preformed acid chloride or anhydride or with the carboxylic acid and a dehydrating agent, such as DCC or EDAC·HCl). Alternately, nitrosation of the ester product containing a deprotected alcohol moiety may be accomplished by first converting the alcohol to a leaving group, such as a mesylate or a tosylate. This reaction is typically performed at a temperature of 0 $^{0}$C to room temperature in an inert solvent, such as ether, THF, or dichloromethane with the alcohol, methansulfonyl chloride or para-toluensulfonyl chloride, and an amine base, such as triethylamine or pyridine, as the reactants.

Scheme 1



1

IA X = ONO
IB X = SNO
IC X= $ONO_2$

The compounds of the invention include the ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, including those described herein, which have been nitrosated and/or nitrosylated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen. The nitrosated and/or nitrosylated ursodeoxycholic acid compound of the invention donate, transfer or release a biologically active form of nitrogen monoxide (i.e., nitric oxide).

Nitrogen monoxide can exist in three forms: NO- (nitroxyl), NO• (uncharged nitric oxide) and $NO^+$ (nitrosonium). NO• is a highly reactive short-lived species that is potentially toxic to cells. This is critical because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to the nitric oxide radical (NO•), nitrosonium ($NO^+$) does not react with $O_2$ or $O_2^-$ species, and functionalities capable of transferring and/or releasing $NO^+$ and NO- are also resistant to decomposition in the presence of many redox metals. Consequently, administration of charged NO equivalents (positive and/or negative) is a more effective means of delivering a biologically active NO to the desired site of action.

Compounds contemplated for use in the invention, e.g., ursodeoxycholic acid compound, or an amide or sulfate conjugate thereof, that can be optionally nitrosated and/or nitrosylated, through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen, are, optionally, used in combination with nitric oxide and compounds that release nitric oxide or otherwise directly or indirectly deliver or transfer a biologically active form of nitrogen monoxide to a site of its intended activity, such as on a cell membrane *in vivo*.

The term "nitric oxide" encompasses uncharged nitric oxide (NO•) and charged nitrogen monoxide species, preferably charged nitrogen monoxide species, such as nitrosonium ion ($NO^+$) and nitroxyl ion (NO-). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitrogen monoxide releasing, delivering or transferring compounds have the structure F-NO, wherein F is a nitrogen monoxide releasing, delivering or transferring moiety, and include any and all such compounds which provide nitrogen monoxide to its intended site of action in a form active for its

intended purpose. The term "NO adducts" encompasses any nitrogen monoxide releasing, delivering or transferring compounds, including, for example, S-nitrosothiols, nitrites, nitrates, S-nitrothiols, sydnonimines, 2-hydroxy-2-nitrosohydrazines, (NONOates), (E)-alkyl-2-((E)- hydroxyimino)-5-nitro-3-hexeneamide (FK-409), (E)-alkyl-2-((E)-hydroxyimino)-5-nitro-3- hexeneamines, N-((2Z, 3E)-4-ethyl-2-(hydroxyimino)-6-methyl-5-nitro-3-heptenyl)-3- pyridinecarboxamide (FR 146801), nitrosoamines, furoxans as well as substrates for the endogenous enzymes which synthesize nitric oxide. NONOates include, but are not limited to, (Z)-1-(N-methyl-N-(6-(N-methyl-ammoniohexyl)amino))diazen-1-ium-1,2-diolate ("MAHMA/NO"), (Z)-1-(N-(3-ammoniopropyl)-N-(n-propyl)amino)diazen-1-ium-1,2-diolate ("PAPA/NO"), (Z)-1-(N-(3-aminopropyl)-N-(4-(3-aminopropylammonio)butyl)-amino) diazen-1-ium-1,2-diolate (spermine NONOate or "SPER/NO") and sodium(Z)-1-(N,N- diethylamino)diazenium-1,2-diolate (diethylamine NONOate or "DEA/NO") and derivatives thereof. NONOates are also described in U.S. Patent Nos. 6,232,336, 5,910,316 and 5,650,447, the disclosures of which are incorporated herein by reference in their entirety. The "NO adducts" can be mono-nitrosylated, poly-nitrosylated, mono-nitrosated and/or poly-nitrosated at a variety of naturally susceptible or artificially provided binding sites for biologically active forms of nitrogen monoxide.

One group of NO adducts is the S-nitrosothiols, which are compounds that include at least one -S-NO group. These compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars; S-nitrosylated, modified and unmodified, oligonucleotides (preferably of at least 5, and more preferably 5-200 nucleotides); straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted S-nitrosylated hydrocarbons; and S-nitroso heterocyclic compounds. S-nitrosothiols and methods for preparing them are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; and Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

Another embodiment of the invention is S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. Such compounds include, for example, S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, S-nitroso-cysteinyl-glycine, and the like.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur groups on an amino acid or amino acid derivative thereof) from various functional classes including enzymes, such as tissue-type plasminogen activator (TPA) and cathepsin B; transport proteins, such as lipoproteins; heme proteins, such as hemoglobin and serum albumin; and biologically protective proteins, such as immunoglobulins, antibodies and cytokines. Such

nitrosylated proteins are described in WO 93/09806, the disclosure of which is incorporated by reference herein in its entirety. Examples include polynitrosylated albumin where one or more thiol or other nucleophilic centers in the protein are modified.

Other examples of suitable S-nitrosothiols include:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; $R_e$ and $R_f$ are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro,

-T-V, or $-(C(R_g)(R_h))_k$-T-V or $R_e$ and $R_f$ taken together are an oxo, a methanthial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group;

V is -NO or $-NO_2$;

T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$, wherein o is an integer from 0 to 2,

k is an integer from 1 to 3;

$R_a$ is a lone pair of electrons, a hydrogen or an alkyl group;

$R_i$ is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2-C(T\text{-}V)(R_g)(R_h)$, or $-(N_2O_2-)^-\bullet M^+$, wherein $M^+$ is an organic or inorganic cation; with the proviso that when $R_i$ is $-CH_2-C(T\text{-}V)(R_g)(R_h)$ or $-(N_2O_2-)\bullet M^+$; then "-T-V'" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and

$R_g$ and $R_h$ at each occurrence are independently $R_e$;

In cases where $R_e$ and $R_f$ are a heterocyclic ring or taken together $R_e$ and $R_f$ are a heterocyclic ring, then $R_i$ can be a substituent on any disubstituted nitrogen contained within the radical wherein $R_i$ is as defined herein.

Nitrosothiols can be prepared by various methods of synthesis. In general, the thiol precursor

is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium tetrafluoroborate in an inert solvent.

Another group of NO adducts for use in the invention, where the NO adduct is a compound that donates, transfers or releases nitric oxide, include compounds comprising at least one ON-O- or ON-N- group. The compounds that include at least one ON-O- or ON-N- group are preferably ON-O- or ON-N-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O- or ON-N-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O- or ON-N-sugars; ON-O- or -ON-N- modified or unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); ON-O- or ON-N- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and ON-O-, ON-N- or ON-C-heterocyclic compounds.

Another group of NO adducts for use in the invention include nitrates that donate, transfer or release nitric oxide, such as compounds comprising at least one $O_2N$-O-, $O_2N$-N- or $O_2N$-S- group. Preferred among these compounds are $O_2N$-O-, $O_2N$-N- or $O_2N$-S- polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); $O_2N$-O-, $O_2N$-N- or $O_2N$-S- amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); $O_2N$-O-, $O_2N$-N- or $O_2N$-S- sugars; $O_2N$-O-, $O_2N$-N- or $O_2N$-S- modified and unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); $O_2N$-O-, $O_2N$-N- or $O_2N$-S- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and $O_2N$-O-, $O_2N$-N- or $O_2N$-S- heterocyclic compounds. Preferred examples of compounds comprising at least one $O_2N$-O-, $O_2N$-N- or $O_2N$-S- group include isosorbide dinitrate, isosorbide mononitrate, clonitrate, erythrityl tetranitrate, mannitol hexanitrate, nitroglycerin, pentaerythritol- tetranitrate, pentrinitrol, propatylnitrate and organic nitrates with a sulfhydryl-containing amino acid such as, for example SPM 3672, SPM 5185, SPM 5186 and those disclosed in U. S. Patent Nos. 5,284,872, 5,428,061, 5,661,129, 5,807,847 and 5,883,122 and in WO 97/46521, WO 00/54756 and in WO 03/013432, the disclosures of each of which are incorporated by reference herein in their entirety.

Another group of NO adducts are N-oxo-N-nitrosoamines that donate, transfer or release nitric oxide and are represented by the formula: $R^{1"}R^{2"}N$-$N(O$-$M^+)$-NO, where $R^{1"}$ and $R^{2"}$ are each independently a polypeptide, an amino acid, a sugar, a modified or unmodified oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and where $M^+$ is an organic or inorganic cation, such as, for

example, an alkyl substituted ammonium cation or a Group I metal cation.

The invention is also directed to compounds that stimulate endogenous NO or elevate levels of endogenous endothelium-derived relaxing factor (EDRF) *in vivo* or are substrates for nitric oxide synthase. Such compounds include, for example, L-arginine, L-homoarginine, and N-hydroxy-L-arginine, including their nitrosated and nitrosylated analogs (e.g., nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine and nitrosylated L-homoarginine), precursors of L-arginine and/or physiologically acceptable salts thereof, including, for example, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids, inhibitors of the enzyme arginase (e.g., N-hydroxy-L-arginine and 2(S)-amino-6-boronohexanoic acid), nitric oxide mediators and/or physiologically acceptable salts thereof, including, for example, pyruvate, pyruvate precursors, α-keto acids having four or more carbon atoms, precursors of α-keto acids having four or more carbon atoms (as disclosed in WO 03/017996, the disclosure of which is incorporated herein in its entirety), and the substrates for nitric oxide synthase, cytokines, adenosin, bradykinin, calreticulin, bisacodyl, and phenolphthalein. EDRF is a vascular relaxing factor secreted by the endothelium, and has been identified as nitric oxide (NO) or a closely related derivative thereof (Palmer et al, *Nature*, 327:524-526 (1987); Ignarro et al, *Proc. Natl. Acad. Sci. USA*, 84:9265-9269 (1987)).

The invention is also based on the discovery that compounds and compositions of the invention may be used in conjunction with other therapeutic agents for co-therapies, partially or completely, in place of other conventional antiinflammatory compounds, such as, for example, together with steroids, NSAIDs, COX-2 inhibitors, 5-lipoxygenase (5-LO) inhibitors, leukotriene $B_4$ ($LTB_4$) receptor antagonists, leukotriene $A_4$ ($LTA_4$) hydrolase inhibitors, 5-HT agonists, HMG-CoA inhibitors, $H_2$ receptor antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opiods, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures of two or more thereof.

Leukotriene $A_4$ ($LTA_4$) hydrolase inhibitors refer to compounds that selectively inhibit leukotriene $A_4$ hydrolase with an $IC_{50}$ of less than about 10μM, and preferably with an $IC_{50}$ of less than about 1 μM. Suitable $LTA_4$ hydrolase inhibitors include, but are not limited to, RP-64966, (S,S)-3-amino-4-(4-benzyloxyphenyl)-2-hydroxybutyric acid benzyl ester, N-(2(R)-(cyclohexylmethyl)-3-(hydroxycarbamoyl)propionyl)-L-alanine, 7-(4-(4-ureidobenzyl)phenyl) heptanoic acid and 3 (3-(1E,3E-tetradecadienyl)-2-oxiranyl)benzoic acid lithium salt, and mixtures of two or more thereof.

Suitable $LTB_4$ receptor antagonists include, but are not limited to, ebselen, linazolast, ontazolast; WAY 121006; Bay-x-1005; BI-RM-270; CGS-25019C; ETH-615; MAFP; TMK-688; T-0757; LY 213024, LY 210073, LY 223982, LY 233469, LY 255283, LY 264086, LY 292728 and LY 293111; ONO-LB457, ONO-4057, and ONO-LB-448, S-2474, calcitrol; PF 10042; Pfizer 105696; RP 66153; SC-53228, SC-41930, SC-50605, SC-51146 and SC-53228; SB-201146 and SB-209247;

SKF-104493; SM 15178; TMK-688; BPC 15, and mixtures of two or more thereof. The preferred $LTB_4$ receptor antagonists are calcitrol, ebselen, Bay-x-1005, CGS-25019C, ETH-615, LY-293111, ONO-4057 and TMK-688, and mixtures of two or more thereof.

Suitable 5-LO inhibitors include, but are not limited to, A-76745, 78773 and ABT761; Bay-x-1005; CMI-392; E-3040; EF-40; F-1322; ML-3000; PF-5901; R-840; rilopirox, flobufen, linasolast, lonapolene, masoprocol, ontasolast, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate, and bunaprolast, and mixtures of two or more thereof. Suitable 5-LO inhibitors are also described more fully in WO 97/29776, the disclosure of which is incorporated herein by reference in its entirety

Suitable 5-HT agonists, include, but are not limited to, rizatriptan, sumatriptan, naratriptan, zolmitroptan, eleptriptan, almotriptan, ergot alkaloids. ALX 1323, Merck L 741604 SB 220453 and LAS 31416. Suitable 5-HT agonists are described more fully in WO 0025779, and in WO 00/48583. 5-HT agonists refers to a compound that is an agonist to any 5-HT receptor, including but not limited to, 5-$HT_1$ agonists, 5-$HT_{1B}$ agonists and 5-$HT_{1D}$ agonists, and the like.

Suitable steroids, include, but are not limited to, budesonide, dexamethasone, corticosterone, prednisolone, and the like. Suitable steroids are described more fully in the literature, such as in the Merck Index on CD-ROM, 13$^{th}$ Edition.

Suitable HMG CoA inhibitors, include, but are not limited to, reductase and synthase inhibitors, such as, for example, squalene synthetase inhibitors, benzodiazepine squalene synthase inhibitors, squalene epoxidase inhibitors, acyl-coenzyme A, bile acid sequestrants, cholesterol absorption inhibitors, and the like. Suitable HMG CoA inhibitors include simvastatin, pravastatin, lovastatin, mevastatin, fluvastatin, atorvastatin, cerivastatin, and the like, and are described more fully in U.S. Patent No. 6,245,797 and WO 99/20110, the disclosures of which are incorporated herein by reference in their entirety.

Suitable NSAIDs, include, but are not limited to, acetaminophen, aspirin, diclofenac, ibuprofen, ketoprofen, naproxen, indomethacin, including but not limited to prodrugs thereof, and the like. Suitable NSAIDs are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 617-657; the Merck Index on CD-ROM, 13$^{th}$ Edition; and in U.S. Patent Nos. 6,057,347 and 6,297,260 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable COX-2 inhibitors, include, but are not limited to, NS-386, nimesulide, flosulide, celecoxib, rofecoxib, COX-189, etoracoxib, Bextra, Dynastat, Arcoxia, SC-57666, DuP 697, SC-58125, SC-58635, and the like, and mixtures of two or more thereof. Suitable COX-2 inhibitors are in U.S. Patent Nos. 5,344,991, 5,380,738, 5,393,790, 5,409,944, 5,434,178, 5,436,265, 5,466,823, 5,474,995, 5,510,368, 5,536,752, 5,550,142, 5,552,422, 5,604,253, 5,604,260, and 5,639,780 and in WO 94/03387, WO 94/15723, WO 94/20480, WO 94/26731, WO 94/27980, WO 95/00501, WO 95/15316, WO 96/03387, WO 96/03388, WO 96/06840, WO 96/21667, WO 96/31509, WO

96/36623, WO 97/14691, WO 97/16435, WO 01/45703 and WO 01/87343; and in STN file registry and phar; the disclosures of each of which are incorporated by reference herein in their entirety. the disclosures of which are incorporated herein by reference in their entirety.

Suitable $H_2$ receptor anatgonists, include, but are not limited to, cimetidine, roxatidine, rantidine and the like. Suitable $H_2$ receptor antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 901-915; the Merck Index on CD-ROM, 13th Edition; and in WO 00/28988 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable antineoplastic agents, include but are not limited to, 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, altretamine, anaxirone, aclarubicin and the like. Suitable antineoplastic agents are also described in U. S. Patent No. 6,025,353 and WO 00/38730, the disclosures of which are incorporated herein by reference in their entirety.

Suitable antiplatelet agents, include but are not limited to, aspirin, ticlopidine, dipyridamole, clopidogrel, glycoprotein IIb/IIIa receptor antagonists, and the like. Suitable antineoplastic agents are also described in WO 99/45913, the disclosure of which is incorporated herein by reference in its entirety. In a preferred embodiment of the invention, the antiplatelet agent is aspirin, more preferably, low-dose aspirin (i.e. 75 mg – 100 mg/day).

Suitable thrombin inhibitors, include but are not limited to, N'-((1-(aminoiminomethyl)-4-piperidinyl)methyl)-N-(3,3-diphenylpropinyl)-L-proline amide),3-(2-phenylethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylene-carboxamidomethylpyridinyl)-2-pyrazinone, 3-(2-phenethylamino)-6-methyl-1-(2-amino-6-methyl-5- methylenecarboxamidomethylpyridinyl)-2-pyridinone, and the like. Suitable thrombin inhibitors are also described in WO 00/18352, the disclosure of which is incorporated herein by reference in its entirety.

Suitable thromboxane inhibitors, include but are not limited to thromboxane synthase inhibitors, thromboxane receptor antagonists, and the like. Suitable thromboxane inhibitors, are also described in WO 01/87343, the disclosure of which is incorporated herein by reference in its entirety.

Suitable decongestants include, but are not limited to, phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine, and the like.

Suitable antitussives include, but are not limited to, codeine, hydrocodone, caramiphen, carbetapentane, dextramethorphan, and the like.

Suitable proton pump inhibitors, include, but are not limited to, omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, and the like. Suitable proton pump inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 901-915; the Merck Index on CD-ROM, 13th Edition; and in WO 00/50037 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

The compounds and compositions of the invention, may also be used in combination therapies with opioids and other analgesics, including, but not limited to, narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, neurokinin 1 receptor antagonists, Substance P antagonists, neurokinin-1 receptor antagonists, sodium channel blockers, N-methyl-D-aspartate receptor antagonists, and mixtures of two or more thereof. Preferred combination therapies would be with morphine, meperidine, codeine, pentazocine, buprenorphine, butorphanol, dezocine, meptazinol, hydrocodone, oxycodone, methadone, Tramadol ((+) enantiomer), DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI-204448, acetominophen (paracetamol), propoxyphene, nalbuphine, E-4018, filenadol, mirtentanil, amitriptyline, DuP631, Tramadol ((-) enantiomer), GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate, Dynorphine A, E-2078, AXC3742, SNX-111, ADL2-1294, ICI-204448, CT-3, CP-99,994, CP-99,994, and mixtures of two or more thereof.

The compounds and compositions of the invention can also be used in combination with inducible nitric oxide synthase (iNOS) inhibitors. Suitable iNOS inhibitors are disclosed in U. S. Patent Nos. 5,132,453 and 5,273,875, and in WO 97/38977 and WO 99/18960, the disclosures of each of which are incorporated by reference herein in their entirety.

The invention is also based on the discovery that the administration of a therapeutically effective amount of the compounds and compositions described herein is effective for treating and/or preventing portal hypertension, liver diseases, reflux, gastritis, inflammatory conditions of the gastrointestinal tract, coronary heart diseases, neurological or cognitive conditions or for lowering cholesterol levels by administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitrosated and/or nitrosylated ursodeoxycholic acid compound. In another embodiment, the patient can be administered a therapeutically effective amount of at least one ursodeoxycholic acid compound, that is optionally nitrosated and/or nitrosylated, and at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one ursodeoxycholic acid compound, that is optionally nitrosated and/or nitrosylated, and, at least one therapeutic agent, including but not limited to, steroids, nonsteroidal antiinflammatory compounds (NSAID), COX-2 inhibitors, 5-lipoxygenase (5-LO) inhibitors, leukotriene $B_4$ ($LTB_4$) receptor antagonists, leukotriene $A_4$ ($LTA_4$) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, $H_2$ antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and, optionally, at least one compound that

donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. The compounds can be administered separately or in the form of a composition.

When administered separately, the ursodeoxycholic acid compound, that is optionally nitrosated and/or nitrosylated, can be administered about the same time as part of the overall treatment regimen, i.e., as a combination therapy. "About the same time" includes administering the ursodeoxycholic acid compound, that is optionally nitrosated and/or nitrosylated, simultaneously, sequentially, at the same time, at different times on the same day, or on different days, as long as they are administered as part of an overall treatment regimen, i.e., combination therapy or a therapeutic cocktail.

When administered in vivo, the compounds and compositions of the invention can be administered in combination with pharmaceutically acceptable carriers and in dosages described herein. When the compounds and compositions of the invention are administered as a combination of at least one ursodeoxycholic acid compound and/or at least one nitrosated and/or nitrosylated COX-2 selective inhibitor and/or at least one nitric oxide donor and/or therapeutic agent, they can also be used in combination with one or more additional compounds which are known to be effective against the specific disease state targeted for treatment. The nitric oxide donors, therapeutic agents and/or other additional compounds can be administered simultaneously with, subsequently to, or prior to administration of the ursodeoxycholic acid compound and/or nitrosated and/or nitrosylated ursodeoxycholic acid compound.

The compounds and compositions of the invention can be administered by any available and effective delivery system including, but not limited to, orally, bucally, parenterally, by inhalation spray, by topical application, by injection, transdermally, or rectally (e.g., by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Transdermal compound administration, which is known to one skilled in the art, involves the delivery of pharmaceutical compounds via percutaneous passage of the compound into the systemic circulation of the patient. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Other components can be incorporated into the transdermal patches as well. For example, compositions and/or transdermal patches can be formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, and the like. Dosage forms for topical administration of the compounds and compositions can include creams, sprays, lotions, gels, ointments, eye drops, nose drops, ear drops, and the like. In such dosage forms, the compositions of the invention can be mixed to form white, smooth, homogeneous, opaque cream or lotion with, for example, benzyl alcohol 1% or 2% (wt/wt) as a preservative, emulsifying

wax, glycerin, isopropyl palmitate, lactic acid, purified water and sorbitol solution. In addition, the compositions can contain polyethylene glycol 400. They can be mixed to form ointments with, for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum, emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical application. The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing.

Solid dosage forms for oral administration can include capsules, tablets, effervescent tablets, chewable tablets, pills, powders, sachets, granules and gels. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the active compounds or compositions of the invention and vegetable oil. Hard gelatin capsules can contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of gelatin. Tablets and pills can be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Suppositories for vaginal or rectal administration of the compounds and compositions of the invention, such as for treating pediatric fever and the like, can be prepared by mixing the compounds or compositions with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at rectal temperature, such that they will melt in the rectum and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. Sterile fixed oils are also conventionally used as a solvent or suspending medium.

The compositions of this invention can further include conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application

which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting agents, emulsifying agents and/or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

Various delivery systems are known and can be used to administer the compounds or compositions of the invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules and the like. The required dosage can be administered as a single unit or in a sustained release form.

The bioavailability of the compositions can be enhanced by micronization of the formulations using conventional techniques such as grinding, milling, spray drying and the like in the presence of suitable excipients or agents such as phospholipids or surfactants.

The preferred methods of administration of the ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, and compositions for the treatment of gastrointestinal disorders are orally, bucally or by inhalation. The preferred methods of administration for the treatment of inflammation and microbial infections are orally, bucally, topically, transdermally or by inhalation.

The compounds and compositions of the invention can be formulated as pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid and the like. Appropriate organic acids include, but are not limited to, aliphatic,

cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, such as, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesuifonic, sulfanilic, stearic, algenic, β-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable pharmaceutically-acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine and the like. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

While individual needs may vary, determination of optimal ranges for effective amounts of the compounds and/or compositions is within the skill of the art. Generally, the dosage required to provide an effective amount of the compounds and compositions, which can be adjusted by one of ordinary skill in the art, will vary depending on the age, health, physical condition, sex, diet, weight, extent of the dysfunction of the recipient, frequency of treatment and the nature and scope of the dysfunction or disease, medical condition of the patient, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound used, whether a drug delivery system is used, and whether the compound is administered as part of a drug combination.

The amount of a given ursodeoxycholic acid compound of the invention that will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques, including reference to Goodman and Gilman, supra; The Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 1995; and Drug Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be used in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided by the physician and the patient's circumstances.

The amount of nitric oxide donor in a pharmaceutical composition can be in amounts of about 0.1 to about 10 times the molar equivalent of the ursodeoxycholic acid compound. The usual daily doses of the ursodeoxycholic acid compounds are about 0.05 mg to about 100 mg/kg of body weight per day, preferably 1 mg to 50 mg/kg per day, or alternatively about 5 mg to about 20 mg per patient per day, depending upon the severity of the disease, the stage of the illness, further diseases of the patient, the administration route and further parameters which are known to one skilled in the art. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, and most preferably once per day. Effective doses may be extrapolated from dose-response

curves derived from *in vitro* or animal model test systems and are in the same ranges or less than as described for the commercially available compounds in the Physician's Desk Reference, supra.

The invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the invention, including, at least, one or more of the the ursodeoxycholic acid compound, or an amide or sulfate conjugate thereof, that is optionally nitrosated and/or nitrosylated, and one or more of the NO donors described herein. Associated with such kits can be additional therapeutic agents or compositions (e.g., steroids, NSAIDs, COX-2 inhibitors, 5-lipoxygenase (5-LO) inhibitors, leukotriene $B_4$ ($LTB_4$) receptor antagonists and leukotriene $A_4$ ($LTA_4$) hydrolase inhibitors, 5-HT agonists, HMG-CoA inhibitors, $H_2$ antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and the like), devices for administering the compositions, and notices in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products which reflects approval by the agency of manufacture, use or sale for humans.

The disclosure of each patent, patent application and publication cited or described in the present specification is hereby incorporated by reference herein in its entirety.

Although the invention has been set forth in detail, one skilled in the art will appreciate that numerous changes and modifications can be made to the invention, and that such changes and modifications can be made without departing from the spirit and scope of the invention.

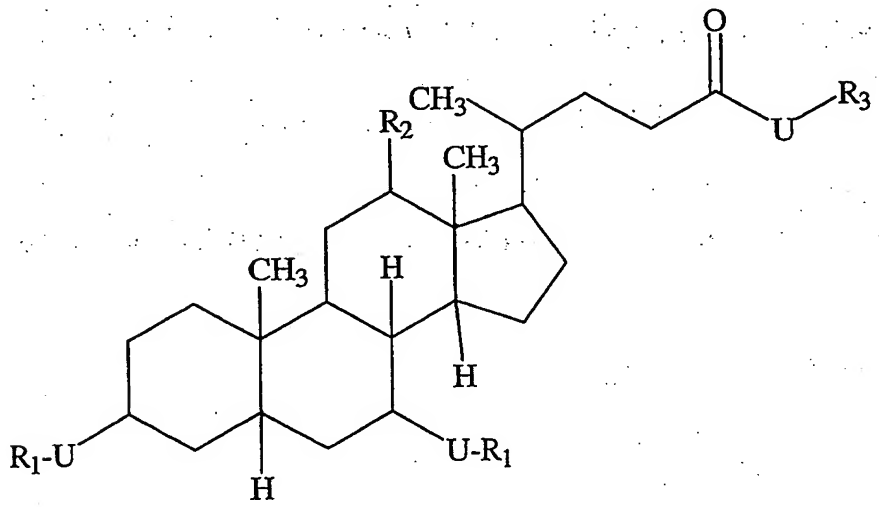
## CLAIMS

What is claimed is:

1. A ursodeoxycholic acid compound comprising at least one NO group, or at least one NO and $NO_2$ group, or a pharmaceutically acceptable salt thereof, wherein the at least one NO group or the at least one NO and $NO_2$ group is linked to the ursodeoxycholic acid compound compound through an oxygen atom, a nitrogen atom or a sulfur atom.

2. The ursodeoxycholic acid compound of claim 1, wherein the ursodeoxycholic acid compound is an amide conjugate or a sulfate conjugate thereof.

3. A compound of Formula (I), or a pharmaceutically acceptable salt thereof. wherein the compound of Formula (I) is:




I

wherein:

$R_1$ is a hydrogen, carboxylic ester group, a lower alkyl group or $D_1$;

$R_2$ is a hydrogen, an alkoxy group or $-OD_1$;

$R_3$ is a hydrogen, a lower alkyl group, V or K;

$D_1$ is a hydrogen, V or K;

V is—NO or $-NO_2$;

U is an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$;

K is $-W_{aa}-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-U-V$;

wherein aa, b, c, d, g, i and j are each independently an integer from 0 to 3;

p, x, y and z are each independently an integer from 0 to 10;

W at each occurrence is independently -C(O)-, -C(S)-, -T-, $-(C(R_e)(R_f))_h-$, an alkyl group, an aryl group, a heterocyclic ring, an arylheterocyclic ring, $-(CH_2CH_2O)_q-$ or a covalent bond;

E at each occurrence is independently a -T- group, an alkyl group, an aryl group, a heterocyclic ring, $-(C(R_e)(R_f))_h-$, an arylheterocyclic ring or $-(CH_2CH_2O)_q-$;

h is an integer form 1 to 10;

q is an integer from 1 to 5;

$R_e$ and $R_f$ are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -U-V, or $-(C(R_g)(R_h))_k$-U-V or $R_e$ and $R_f$ taken together are an oxo, a thial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group;

$R_g$ and $R_h$ at each occurrence are independently $R_e$;

k is an integer from 1 to 3;

T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$,

o is an integer from 0 to 2,

$R_a$ is a lone pair of electrons, a hydrogen or an alkyl group;

$R_i$ is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-OR'_i$, $-CH_2-C(U-V)(R_g)(R_h)$, a bond to an adjacent atom creating a double bond to that atom or $-(N_2O_2-)^-\bullet M^+$, wherein $M^+$ is an organic or inorganic cation; with the proviso that when $R_i$ is $-CH_2-C(U-V)(R_e)(R_f)$ or $-(N_2O_2-)\bullet M^+$; then "-T-V" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group;

$R'_i$ is independently selected from $R_i$; and

with the proviso that the compounds of Formula I must contain least one of a nitrite, a nitrate, a thionitrite ester or a thionitrate ester; and

with the further proviso that the compounds of Formula (I) do not include the compounds of ACS registry numbers 510728-21-9, 349487-19-0, 349481-67-0, 294191-01-8, 301828-27-3, 301828-26-2, 294191-01-8, 124119-82-0, 122387-47-7, 122387-37-5, 120910-03-4, 120498-93-3, 117884-50-1, 103005-02-3, 64219-17-6, 15241-87-9, 15073-15-1, 14943-00-1, 14942-97-3, 14942-96-2, 14942-93-9.

4. The compound of claim 3, wherein the compound of Formula (I) is an amide conjugate or a sulfate conjugate.

5. A composition comprising the compound of claim 3 and a pharmaceutically

acceptable carrier.

6. A method for treating portal hypertension, a liver disease, reflux, gastritis, an inflammatory condition of the gastrointestinal tract, a coronary heart disease, a neurological or cognitive condition or for lowering cholesterol levels in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 5.

7. The method of claim 6, wherein the liver disease is a liver fibrosis, hepatitis, biliary calculosis, biliary dyscinesia, nonalcoholic steatohepatitis, an alcoholic liver disease, Wilson's disease, an acute liver failure, a chronic liver injury, a cholestatic liver disease, cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis or autoimmune cholangitis.

8. The method of claim 6, wherein the inflammatory condition of the gastrointestinal tract is a colon cancer, a rectum cancer, a neoplasm of the colon, a neoplasm of the rectum, a carcinogenesis of the colon, a carcinogenesis of the rectum, an ulcerative colitis, an adenomatous polyp or a familial polyposis.

9. The method of claim 6, wherein the neurological or cognitive condition is a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, AIDs-induced dementia, epilepsy, alcoholism, alcohol withdrawal, drug-induced seizures, a viral, bacterial or fever-induced seizure, trauma to the head, hypoglycemia, hypoxia, a myocardial infarction, a cerebral vascular hemorrhage, a hemorrhage, dementia, a drug-induced brain damage or aging.

10. The composition of claim 5, further comprising at least one therapeutic agent.

11. The composition of claim 10, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a cyclooxygenase-2 inhibitor, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene $B_4$ receptor antagonist, a leukotriene $A_4$ hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a $H_2$ antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

12. A method for treating portal hypertension, a liver disease, reflux, gastritis, an inflammatory condition of the gastrointestinal tract, a coronary heart disease, a neurological or cognitive condition or for lowering cholesterol levels in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 10.

13. The method of claim 12, wherein the liver disease is a liver fibrosis, hepatitis, biliary calculosis, biliary dyscinesia, nonalcoholic steatohepatitis, an alcoholic liver disease, Wilson's disease, an acute liver failure, a chronic liver injury, a cholestatic liver disease, cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis or autoimmune cholangitis.

14. The method of claim 12, wherein the inflammatory condition of the gastrointestinal

tract is a colon cancer, a rectum cancer, a neoplasm of the colon, a neoplasm of the rectum, a carcinogenesis of the colon, a carcinogenesis of the rectum, an ulcerative colitis, an adenomatous polyp or a familial polyposis.

15. The method of claim 12, wherein the neurological or cognitive condition is a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, AIDs-induced dementia, epilepsy, alcoholism, alcohol withdrawal, drug-induced seizures, a viral, bacterial or fever-induced seizure, trauma to the head, hypoglycemia, hypoxia, a myocardial infarction, a cerebral vascular hemorrhage, a hemorrhage, dementia, a drug-induced brain damage or aging.

16. A composition comprising at least one compound of claim 4 and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

17. The composition of claim 16, further comprising a pharmaceutically acceptable carrier.

18. The composition of claim 16, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

19. The composition of claim 18, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, or S-nitroso-cysteinyl-glycine.

20. The composition of claim 18, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; $R_e$ and $R_f$ are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro,

-T-V-, or $-(C(R_g)(R_h))_k$-T-V or $R_e$ and $R_f$ taken together are an oxo, a methanthial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group;

V is -NO or -$NO_2$;

T is independently a covalent bond, a carbonyl, an oxygen, -$S(O)_o$- or -$N(R_a)R_i$-, wherein o is an integer from 0 to 2;

k is an integer from 1 to 3;

$R_a$ is a lone pair of electrons, a hydrogen or an alkyl group;

$R_i$ is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, -$CH_2$-C(T-V)($R_g$)($R_h$), or -($N_2O_2$-)$^-$•$M^+$, wherein $M^+$ is an organic or inorganic cation; with the proviso that when $R_i$ is -$CH_2$-C(T-V)($R_g$)($R_h$) or -($N_2O_2$-)•$M^+$; then "-T-V'" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and $R_g$ and $R_h$ at each occurrence are independently $R_e$.

21. The composition of claim 16, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine, nitrosylated L-homoarginine), citrulline, ornithine, glutamine, lysine, an arginase inhibitor or a nitric oxide mediator.

22. The composition of claim 16, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O- or ON-N- group;

(ii) a compound that comprises at least one $O_2N$-O-, $O_2N$-N- or $O_2N$-S- or group;

(iii) a N-oxo-N-nitrosoamine having the formula: $R^{1''}R^{2''}$N-N(O-$M^+$)-NO, wherein $R^{1''}$ and $R^{2''}$ are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and $M^+$ is an organic or inorganic cation.

23. The composition of claim 22, wherein the compound comprising at least one ON-O- or ON-N- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, an ON-O-heterocyclic compound or an ON-N-heterocyclic compound.

24. The composition of claim 22, wherein compound comprising at least one

$O_2N$-O-, $O_2N$-N- or $O_2N$-S- group is an $O_2N$-O-polypeptide, an $O_2N$-N-polypeptide, an $O_2N$-S-polypeptide, an $O_2N$-O-amino acid, $O_2N$-N-amino acid, $O_2N$-S-amino acid, an $O_2N$-O-sugar, an $O_2N$-N-sugar, $O_2N$-S-sugar, an $O_2N$-O-oligonucleotide, an $O_2N$-N-oligonucleotide, an $O_2N$-S-oligonucleotide, , a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted $O_2N$-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted $O_2N$-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted $O_2N$-S-hydrocarbon, an $O_2N$-O-heterocyclic compound, an $O_2N$-N-heterocyclic compound or an $O_2N$-S-heterocyclic compound.

27. The composition of claim 16, further comprising at least one therapeutic agent.

28. The composition of claim 27, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a cyclooxygenase-2 inhibitor, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene $B_4$ receptor antagonist, a leukotriene $A_4$ hydrolase inhibitor, a 5-HT agonist, a HMG CoA inhibitor, a $H_2$ antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

29. A method for treating portal hypertension, a liver disease, reflux, gastritis, an inflammatory condition of the gastrointestinal tract, a coronary heart disease, a neurological or cognitive condition or for lowering cholesterol levels in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 17 or 27.

30. The method of claim 29, wherein the liver disease is a liver fibrosis, hepatitis, biliary calculosis, biliary dyscinesia, nonalcoholic steatohepatitis, an alcoholic liver disease, Wilson's disease, an acute liver failure, a chronic liver injury, a cholestatic liver disease, cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis or autoimmune cholangitis.

31. The method of claim 29, wherein the inflammatory condition of the gastrointestinal tract is a colon cancer, a rectum cancer, a neoplasm of the colon, a neoplasm of the rectum, a carcinogenesis of the colon, a carcinogenesis of the rectum, an ulcerative colitis, an adenomatous polyp or a familial polyposis.

32. The method of claim 29, wherein the neurological or cognitive condition is a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, AIDs-induced dementia, epilepsy, alcoholism, alcohol withdrawal, drug-induced seizures, a viral, bacterial or fever-induced seizure, trauma to the head, hypoglycemia, hypoxia, a myocardial infarction, a cerebral vascular hemorrhage, a hemorrhage, dementia, a drug-induced brain damage or aging.

33. A kit comprising at least one compound of claim 1.

34. The kit of claim 33, further comprising (i) at least one compound that donates,

transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; (ii) at least one therapeutic agent; or (iii) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent.

35. The kit of claim 34, wherein the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; the at least one therapeutic agent; or the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent; are in the form of separate components in the kit

36. A kit comprising the composition of claim 10, 16 or 27.

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(54) Title: NITROSATED AND/OR NITROSYLATED URSODEOXYCHOLIC ACID COMPOUNDS, COMPOSITIONS AND METHODS OF USE

(57) Abstract: The invention describes nitrosated and/or nitrosylated ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, and novel compositions comprising at least one nitrosated and/or nitrosylated ursodeoxycholic acid compounds, or an amide or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or at least one therapeutic agent. The invention also provides novel compositions comprising at least one ursodeoxycholic acid compound, or an made or sulfate conjugate thereof, or pharmaceutically acceptable salts thereof, and at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or at least one therapeutic agent. The invention also provides novel kits comprising at least one ursodeoxycholic acid compound, that is optionally nitrosated and/or nitrosylated, and, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent. The invention also provides methods for treating and/or preventing portal hypertension, liver diseases, reflux, gastritis, inflammatory conditions of the gastrointestinal tract, coronary heart diseases, neurological or cognitive conditions or for lowering cholesterol levels.

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A. CLASSIFICATION OF SUBJECT MATTER

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | SHUKER. D. E.G. et al. N-Nitroso Bile Acid Conjugates. 1. Synthesis, Chemical Reactivity, and Mutagenic Activity. J. Org. Chem. 1981, Vol. 46, No. 27, pages 2092-2096. See entire document especially Scheme 1, and Table I. | 1-36 |
| X | DIAS. J.R. Masss Spectra of Nitrate Esters of Cholic Acid Derivatives. J. Org. Chem. 1979, Vol. 44, No. 25, pages 4572-4577, entire document. | 1-4 |

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